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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/846,588	Applicant(s) GOLDMAN ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-20,22-24,27-39,41-46 and 48* is/are pending in the application.

4a) Of the above claim(s) *10-12,22-24,31,32 and 41-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,13-20,27-30,33-39,44-46 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on 12/20/02 in Paper No. 11 has been entered.

Claims 1-8, 10-20, 22-24, 27-39, 41-46 and 48 are pending in the present application.

Applicants elected with traverse the invention of Group I with Huntington's disease as a neurodegenerative disease in the method of treatment as a separate group, as well as basal ganglia of the brain as a species for the site to which neurons are recruited to in Paper No. 7 dated 4/9/02 was acknowledged.

Upon reconsideration, the species restriction for the site to which neurons are recruited to is withdrawn by the Examiner.

This application contains claims 10-12, 22-24, 31-32, and 41-43 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Accordingly, claims 1-8, 13-20, 27-30, 33-39, 44-46 and 48 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Objections

Claim 27 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the limitation "wherein recruitment of neurons is to the cortex" in claim 27 is unrelated to the limitation "to recruit neurons to any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" recited in claim 13 from which claim 27 is dependent upon.

Following is a new ground of rejection necessitated by Applicants' amendment.

Claim Rejections - 35 USC § 112

Amended claims 28-30, 33-39 and 44-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for the same reasons set forth in the previous Office Action.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, claims 28-30 and 33-39 are drawn to a method of treating Huntington's disease comprising: providing a nucleic acid construct encoding a neurotrophin and injecting the nucleic acid construct into a subject's lateral ventricles or ventricular zone wall under conditions effective to treat Huntington's disease. Amended claims 44-46 are directed to a method of treating Huntington's disease comprising providing a neurotrophin and introducing the neurotrophin into any one or all of a subject's caudate nucleus, putamen, and/or globus pallidus under conditions effective to treat Huntington's disease.

The specification teaches by exemplification the construction of a replication defective recombinant adenovirus pAd5-CMV:BDNF:IRES:hGFP expressing brain-derived neurotrophic factor (BDGF) under CMV control and humanized green fluorescent protein (hGFP) under internal ribosomal entry site control. The recombinant adenovirus was injected into the lateral ventricles of adult rats that were treated for 18 days thereafter with the mitotic marker bromodeoxyuridine (BrdU). Three weeks after injection, ELISA analysis revealed that the cerebral synovial fluid BDNF level of AdBDNF-injected animals was about 1 ug/g, whereas BDNF was undetectable in cerebral synovial fluid (CSF) of control animals. *In situ* hybridization revealed that BDNF and GFP mRNAs were largely restricted to the ventricular wall (ependymal surface). In AdBDNF-injected rats, the olfactory bulb exhibited a 2.44-fold increase in the number of BrdU+-βIII tubulin+ neurons relative to AdNull (AdCMV:hGFP) controls. Additionally, ventricular AdBDNF infection also induced neuronal recruitment to the neostriatum as evidenced by the presence of BrdU+-βIII tubulin+ neurons, many of

which also expressed glutamic acid decarboxylase, cabindin-D28 and DARPP-32, markers of medium spiny neurons of the neostriatum. These newly generated neurons survived at least 5-8 weeks after viral induction.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention which is drawn to a method of treating Huntington's disease by injecting a nucleic acid construct encoding a neurotrophin or a neurotrophin into a subject's lateral ventricles or ventricular zone wall under conditions effective to treat said disease for the reasons to be discussed below.

(a) The breadth of the claims. With respect to the elected invention, claims 28-30 and 33-39 drawn to a method of treating encompassing delaying, slowing, abrogating and reverse the progression of the Huntington's disease using a nucleic acid construct encoding for any neurotrophic factor, whereas the amended claims 44-46 drawn to a method of treating Huntington's disease comprising providing any neurotrophin and introducing the neurotrophin into any one or all of a subject's caudate nucleus, putamen, and/or globus pallidus under conditions effective for the treatment.

(b) The state of the prior art and the unpredictable of the prior art. At the effective filing date of the present application (05/01/2000), the art for treating any neurodegenerative disease using *in vivo* gene therapy or any neurotrophic factor remains immature and unpredictable with respect to the attainment of therapeutic effects, let alone for treating specifically Huntington's disease. This is evidenced by the reviews of During et al. (Mol. Med. Today 4:485-493, 1998) and Shihabuddin et al. (Mol. Med. Today 5:474-480, 1999). During et al. stated "Which neurological disease are the

best targets for gene therapy, given that currently targeted neurological diseases are determined largely by the availability of animal models and might not be the most responsive to a gene therapy approach?" and "How well do current animal models of central nervous system (CNS) disease predict clinical efficacy of novel therapeutic strategies?" (page 490, in "The outstanding questions"). With respect to claims drawn to *in vivo* gene therapy, it is also well known in the art that the lack of optimal vectors, the lack of stable *in vivo* transgene expression as well as the adverse host immune responses against delivered vectors are some of factors limiting the effectiveness of gene therapy to achieving therapeutic effects. With respect to claims drawn to a method of treating a Huntington's disease by introducing any neurotrophic factor into any one or all of a subject's caudate nucleus, putamen and/or globus pallidus, it is well known in the art that central nervous system (CNS) neurons lack intrinsic ability to mount a regenerative response, particularly in a post-natal or an adult subject (Jackowski; British Journal or Neurology 9:3030-317, 1995). Additionally, it is not known in the art the specific recited brain regions contain any stem cell or progenitor cell population that is capable of responding to any delivered neurotrophic factor in a manner that yields the therapeutic effects for treating Huntington's disease as contemplated by Applicants (see Shihabuddin et al., section titled "Location and identity of progenitors").

(c) The amount of direction or guidance provided. As the term "treatment" encompasses delaying, slowing, abrogating and reverse the progression of the Huntington's disease, the instant specification fails to offer any guidance for a skilled

artisan on how to achieve any of the aforementioned therapeutic effects. There is no correlation between the reported presence of BrdU+-βIII tubulin+ neurons in the neostriatum with any of the therapeutic effects contemplated by Applicants. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so. With the lack of guidance provided by the present disclosure and in light of the totality of the state of the art as discussed above, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed. This is because there is no evidence of record indicating or suggesting that an efficient number of striated neurons in the appropriate location of the brain has been generated to yield any therapeutic effects. Additionally, it is unclear whether these newly induced striated neurons can form functional junctions with preexisting neurons or that these newly generated striated neurons can survive better than the neurons they intend to replace for any significant period of time under the disease conditions to yield any desired therapeutic effects. The present disclosure also fails to provide any *in vivo* example (part of guidance) showing any therapeutic effects has been attained or achieved.

The instant claims encompass the use of any neurotrophins for attaining therapeutic effects in the treatment of Huntington's disease. The instant specification is not enabled for such a claimed invention. Again, neither the instant specification nor the prior art at the effective filing date of the present application teach that other members of the neurotrophin family such as neurotrophin-3, neurotrophin-4, neurotrophin-6, nerve growth factor (NGF) are also capable of effecting neurogenesis in post-natal and adult

brain to the same extent as shown for brain derived neurotrophic factor (BDNF), let alone for attaining any therapeutic effects. Kirschenbaum et al. (Proc. Natl. Acad. Sci. USA 92:210-214, 1995) teach that BDNF is the only neurotrophin tested (BDNF, neurotrophin-3, NGF) that can affect the differentiation and survival of newly generated neurons in the adult rat brain *in vitro* (see abstract and Table 1). The enhanced neuronal survival property of BDNF is also controversial since Ahmed et al. (J. Neurosci. 15:5765-5778, 1995) have demonstrated that BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronal precursors (see abstract). It should also be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

As such, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

With respect to amended claims 44-46, in addition to the issues discussed above, there is no teaching regarding on how an effective amount of any neurotrophin can be maintained in the specific recited brain regions for a sufficient period of time to elicit the desired therapeutic effects or whether the recited brain regions do contain any stem cell or progenitor cell population that is capable of responding to any delivered

neurotrophic factor in a manner (e.g., induced proliferation and differentiation into proper neuron populations) that yields the therapeutic effects for treating Huntington's disease as contemplated by Applicants. As such, with the lack of sufficient guidance provided by the instant specification and in light of the totality of the state of the art discussed above, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Accordingly, due to the lack of direction or guidance provided by the specification regarding to the issues set forth above, the unpredictability of the gene therapy art and physiological art, particularly for attaining therapeutic effects in treating Huntington's disease, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

Response to Arguments

Applicants rely mainly on Dr. Steven A. Goldman's Declaration in responding to the above rejection in the Amendment filed 12/20/02 in Paper No. 11 (pages 5-8).

The Declaration of Dr. Steven A. Goldman has been fully considered. However, it is not found to be persuasive for overcoming the above rejection for the following reasons.

Firstly, there is no factual evidence provided indicating that any therapeutic effects such as delaying, slowing, abrogating and reverse the progression of the Huntington's disease in any subject, including in the R6/2 mouse model has been attained or achieved. The simple determination of >140 new medium spiny

neurons/mm^3/2-3 weeks in the huntingtin mutant R6/2 mouse brain in response to AdBDNF infection of the ventricular zone, and the expected formation of new medium spiny neurons at 2,400-3,640/ mm^3/year or postulated induction of this cell type could slow or reverse the disease progression are not deemed to correlate to the therapeutic effects contemplated by Applicants. This is because that it is still unclear whether an efficient number of striated neurons in the appropriate location of the brain could be eventually generated to yield any therapeutic effects. It is also unclear whether these newly induced striated neurons can form functional junctions with preexisting neurons or that these newly generated striated neurons can survive better than the neurons they intend to replace for any significant period of time under the disease conditions to yield the desired therapeutic effects. In the absence of the guidance provided by the present application, an in light of the totality of the state of the art for treating Huntington's disease discussed above, it would have required undue experimentation for a skilled artisan to make and use the treatment methods as claimed. Particularly, Applicants have also submitted on record that "While there are some therapies available to treat the symptoms and decrease the severity of such diseases (e.g., L-dopa to treat Parkinson's disease), there currently exists no effective treatment to prevent or reduce the degeneration of most of the above-mentioned classes of affected neurons, or to promote their repair" (see page 4 of the Amendment).

Secondly, the statement "I believe that this demonstration of the inducibility of endogenous neural progenitor cells provides us both a conceptual and operational basis for using neurotrophins besides BDNF, as well as gene delivery of such other

neurotrophins, to stimulate endogenous progenitor cells of the adult brain, for the purpose of regenerating neural cell populations lost to disease or injury" is not deemed to be factual evidence indicating that other members of the neurotrophin family such as neurotrophin-3, neurotrophin-4, neurotrophin-6, nerve growth factor (NGF) are also capable of effecting neurogenesis in post-natal and adult brain to the same extent and in the same manner as shown for brain derived neurotrophic factor (BDNF), let alone for attaining any therapeutic effects, and especially in light of the teachings of Kirschenbaum et al. (Proc. Natl. Acad. Sci. USA 92:210-214, 1995) and Ahmed et al. (J. Neurosci. 15:5765-5778, 1995) regarding to the variation in the biological effects among members of the neurotrophin family. The results of the post-filing art of Nakatomi et al. are not relevant to the presently claimed invention because FGF is not a member of the neurotrophin family. Furthermore, with respect to the breadth of using any members of the neurotrophin family for treating Huntington's disease in the claimed methods, Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, claims 28-30, 33-39 and 44-46 are rejected under 35 U.S.C. 112, first paragraph for the reasons set forth above.

Amended claims 1-8, 13-20 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing neuronal production or recruiting neurons to a subject's olfactory bulb and neostriatum in post-natal and adult brain comprising: providing a nucleic acid construct encoding a brain derived neurotrophic factor (BDNF) and injecting the nucleic acid construct into a subject's lateral ventricles or ventricular zone wall under conditions effective to express the BDNF and to induce neuronal production or to recruit neurons to said subject's olfactory bulb and neostriatum, does not reasonably provide enablement for a method of inducing neuronal production or recruiting neurons to the globus pallidus of the subject or a method of inducing neuronal production or recruiting neurons to a subject's brain using a nucleic acid construct encoding any neurotrophins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Action.

With respect to the elected invention, claims 1-8 are directed to a method of inducing neuronal production in post-natal and adult brain and spinal cord comprising: providing a nucleic acid construct encoding a neurotrophin and injecting the nucleic acid construct into a subject's lateral ventricles or ventricular zone wall under conditions effective to express the neurotrophin and to induce neuronal production in any one or all

of the caudate nucleus, the putamen, and/or the globus pallidus of the subject. Claims 13-20 and 27 are directed to a method of recruiting neurons to a subject's brain comprising: providing a nucleic acid construct encoding a neurotrophin and injecting the nucleic acid construct into the subject's lateral ventricles or ventricular zone wall under conditions effective to express the neurotrophin and to recruit neurons to any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject.

The instant claims encompass the induction of neuronal production or recruiting neurons in both post-natal and adult brain using any neurotrophins, the instant specification is not enabled for such a broadly claimed invention. As already noted above neither the instant specification nor the prior art at the effective filing date of the present application teach that other members of the neurotrophin family such as neurotrophin-3, neurotrophin-4, neurotrophin-6, nerve growth factor (NGF) are also capable of effecting neurogenesis in post-natal and adult brain to the same extent as shown for brain derived neurotrophic factor (BDNF). Kirschenbaum et al. (Proc. Natl. Acad. Sci. USA 92:210-214, 1995) teach that BDNF is the only neurotrophin tested (BDNF, neurotrophin-3, NGF) that can affect the differentiation and survival of newly generated neurons in the adult rat brain *in vitro* (see abstract and Table 1). The enhanced neuronal survival property of BDNF is also controversial since Ahmed et al. (J. Neurosci. 15:5765-5778, 1995) have demonstrated that BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronal precursors (see abstract). It should be noted that the physiological art is recognized as unpredictable

(MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

As such, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

The instant claims also encompass a method of inducing neuronal production and recruiting neurons to the globus pallidus of the subject as well as to the cortex (specifically for claim 27) using any neurotrophins, the instant specification is not enabled for such a broadly claimed invention. Apart from the exemplification showing an increased neuronal production and recruitment to the olfactory bulb and to a lesser extent to the neostriatum (the striatum consists of the caudate and putamen; see Weiss et al., U.S. Patent No. 6,071889, col. 3, lines 39-40) by injecting a replication defective recombinant adenovirus expressing BDNF into the lateral ventricles of adult rats, there is no evidence indicating that any significant number of induced neurons has been generated (in comparison with proper control animals) in the globus pallidus region or in the cortex region by BDNF, let alone by any other neurotrophins. Applicants are invited to point out the specific page numbers and line numbers where the neuronal production and/or recruitment to the specific aforementioned brain regions has been attained or achieved. On the contrary, Applicants specifically teach that only very rare BrdU+/β-III-

tubulin+ neuron were found in the frontal cortex of AdBDNF-treated animals, too few to merit systematic comparison to null controls (see specification on page 35, lines 12-14). Since the prior art at the effective filing date of the present application does not provide such guidance, and in light of the complexity of the brain physiology and the unpredictability in the migration of any brain cell population to the specific recited brain regions, it is incumbent upon the instant specification to do so. Again, with the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the full scope of the methods as claimed.

Accordingly, due to the lack of direction or guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants rely mainly on Dr. Steven A. Goldman's Declaration in responding to the above rejection in the Amendment filed 12/20/02 in Paper No. 11 (pages 5-8).

The Declaration of Dr. Steven A. Goldman has been fully considered. However, it is not found to be persuasive for overcoming the above rejection because the disclosure that >40% of the newly generated striatal neurons extended fibers to the globus pallidus is not an evidence that neuronal production or recruitment of neurons to

the globus pallidus of a subject in response to AdBDNF infection of the ventricular zone has been obtained in the methods as claimed.

Accordingly, amended claims 1-8, 13-20 and 27 are rejected under 35 U.S.C. 112, first paragraph for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 is dependent on the cancelled claim 26, therefore it is unclear what exactly Applicants want to claim. The metes and bounds of the claim are not clearly determined.

Claim Rejections - 35 USC § 102

Amended claims 1-5, 7, 13-17 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss et al. (U.S. Patent No. 6,071,889 with an effective filing date of 6/7/1995).

Weiss et al. teach a method comprising the step of administering (including injection) a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral ventricle of the forebrain, of a mammal (juvenile and adult) for inducing the proliferation and differentiation of neural stem cells *in vivo* (see

Summary of Invention, cols. 26-29; col. 27, lines 3-11; and the claims). Weiss et al. also disclose that any expression vector known in the art can be used to express BDNF as long as it has a promoter that is active in the cell, and appropriate termination and polyadenylation signals. Expression vectors such as retroviral vectors, adenovirus vectors, adeno-associated virus vectors, HSV vectors, vaccinia virus vectors and others (col. 29, lines 44-57; col. 20, lines 61-63); mammalian cell specific promoters such as those of tyrosine hydroxylase, DBH, GFAP, NSE, NF, phenylethanolamine N-methyltransferase as well as retroviral LTR, SV40 and CMV promoters can be utilized (col. 29, lines 17-25). Weiss et al. specifically teach that the infected subependymal cells migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40).

Since the teachings of Weiss et al. meet every limitation of the instant claims, Weiss et al. anticipate the instant claimed invention.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed 12/20/02 in Paper No. 11 (page 8) has been fully considered.

Applicants argue mainly that Weiss fails to teach injecting a nucleic acid construct encoding a neurotrophic factor into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production or recruit neurons to in any one or all of the caudate nucleus, the

putamen and/or the globus pallidus of the subject. Applicants' argument is respectfully found to be unpersuasive because Weiss et al. teach a method comprising a step of administering (including injection) a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral ventricle of the forebrain, of a mammal (juvenile and adult) to induce the proliferation and differentiation of neural stem cells *in vivo* (see Summary of Invention, cols. 26-29; col. 27, lines 3-11; and the claims). Furthermore, Weiss et al. specifically teach that the infected subependymal cells migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40).

Amended claims 1-4, 7, 13-16 and 19 are rejected under 35 U.S.C. 102(a) as being anticipated by Benraiss et al. (Society for Neuroscience 25, 413.3, 1999) as evidenced by Weiss et al. (U.S. Patent No. 6,071,889 with an effective filing date of 6/7/1995).

Benraiss et al. teach a single lateral ventricular injection of a BDNF-expressing adenovirus under the control of a CMV promoter substantially augmented the recruitment of new neurons into the olfactory bulbs of an adult rat brain in comparison with the controlled animals (see the abstract). Since Benraiss et al. teach a method having the same steps and the same starting materials as the presently claimed invention, it is inherently that neuronal production in post-natal and adult brain as well as the recruitment of neurons to the caudate nucleus and the putamen would also be

obtained as evidenced by the teachings of Weiss et al. who showed that the subependymal cells that are infected by the same method migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40).

Therefore, Benraiss et al. anticipate the instant claims.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed 12/20/02 in Paper No. 11 (pages 8-9) has been fully considered.

Applicants argue mainly that Benraiss fails to teach injecting a nucleic acid construct encoding a neurotrophic factor into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production or recruit neurons in any one or all of the caudate nucleus, the putamen and/or the globus pallidus of the subject. Applicants' argument is respectfully found to be unpersuasive because Benraiss et al. teach a method having the same steps and the same starting materials as the presently claimed invention, it is inherently that neuronal production in post-natal and adult brain as well as the recruitment of neurons to the caudate nucleus and the putamen would also be obtained as evidenced by the teachings of Weiss et al. who showed that the subependymal cells that are infected by the same method migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40).

Furthermore, it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. In re Woodruff, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); In re Swinehart, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and Ex Parte Novitski, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

Claim Rejections - 35 USC § 103

Amended claims 1, 6, 13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Weiss et al. (U.S. Patent No. 6,071,889 with an effective filing date of 6/7/1995) in view of Reeves (U.S. Patent No. 5,965,440).

Within the enabled scope of the presently claimed invention, Weiss et al. teach a method comprising a step for administering (including injection) a nucleic acid sequence comprising a sequence encoding BDNF into a CNS ventricle, specifically the lateral ventricle of the forebrain, of a mammal (juvenile and adult) for inducing the proliferation and differentiation of neural stem cells *in vivo* (see Summary of Invention, cols. 26-29; col. 27, lines 3-11; and the claims). Weiss et al. also disclose that any expression vector known in the art can be used to express BDNF as long as it has a promoter that is active in the cell, and appropriate termination and polyadenylation signals. Expression vectors such as retroviral vectors, adenovirus vectors, adeno-associated virus vectors, HSV vectors, vaccinia virus vectors and others (col. 29, lines 44-57; col. 20, lines 61-63); mammalian cell specific promoters such as those of tyrosine hydroxylase, DBH, GFAP, NSE, NF, phenylethanolamine N-methyltransferase as well

as retroviral LTR, SV40 and CMV promoters can be utilized (col. 29, lines 17-25). Weiss et al. specifically teach that the infected subependymal cells migrate out into the striatum where they differentiate into neuronal cells (see col. 28, lines 48-51; col. 50, lines 49-55), and that the striatum consists of the caudate and putamen (see col. 3, lines 39-40).

However, Weiss et al. do not specifically teach the use of any inducible or conditional promoter for expressing BDNF.

However, at the effective filing date of the present application Reeves already teaches the use of an inducible promoter, specifically a tetracycline regulated promoter, in a retroviral vector system for expressing a gene (e.g., glial derived neurotrophic factor, tyrosine hydroxylase) in a mammalian cell, including *in vivo* (see abstract and Summary of the Invention). Reeves further teaches that the disclosed retroviral tetracycline regulated system enhances the temporal and quantitative control of gene product delivery, as well as a more precise induction of gene expression relative to other tetracycline-regulated systems known in the art (col. 6, lines 2-16).

Accordingly, at the effective filing date of the present application it would have been obvious and within the level of skills for an ordinary skilled artisan to modify the method taught by Weiss et al. by utilizing an inducible promoter in a retroviral vector for expressing BDNF based on the system taught by Reeves. An ordinary skilled artisan would have been motivated to make this modification because as taught by Reeves the disclosed retroviral tetracycline regulated system enhances the temporal and quantitative control of gene product delivery (and therefore the biological effects of the

delivered gene product, for this instance BDNF), as well as a more precise induction of gene expression relative to other tetracycline-regulated systems known in the art (col. 6, lines 2-16).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER